REMARKS

The current status of the claims is:

Claims 1, 4, 10, 12, 14, 18-20, and 22 are pending in the application.

Claims 2-3, 5-9, 11, 13, 15-17, and 21 were canceled by previous amendment. Claims 2-3, 5-9, 11, 13, and 21 are canceled by this amendment.

Claims 12, 14, and 19 remain in their original form.

Claims 1, 18, and 20 currently amended.

Claims 4 and 10 were previously presented.

Claim 22 is new.

Claim 1 has been amended to recite "orally or systemically" administering to a subject. The "orally or systemically" language was added to claim 1 in the response to Office Action dated May 2, 2007, but was inadvertently omitted in our immediately prior response. Support for this change is found at least at page 15, paragraph 2. Independent claims 18 and 20 have also been amended to recite "orally or systemically" administering chelerythrine to a subject.

Claims 1 and 18 have been amended to remove "salt or polymorph."

Claim 20 as has been amended to delete the word "a" before "chelerythrine."

Support for Claim 22 is found in the specification as filed. For example support is found in the Summary of Invention section, paragraph 1, which states "Additionally, the invention provides compositions and methods useful in treating a subject suffering from a CNS disorder, particularly a CNS disorder associated with impaired prefrontal cortical function related to activation of protein kinase C due to exposure to uncontrollable stress." Support for Claim 22 is also found in the figures, particularly Figures 7 – 9 and 11 which show that stress causes prefrontal cortical dysfunction resulting in working memory deficits. Figures 7-9 and 11 also show that chelerythrine ameliorates stress-induced working memory deficits in rats and monkeys when directly infused into brain, given systemically, or given orally.

Claims are cancelled without prejudice to their assertion in continuation applications.

Claims Rejections Under 35 USC 112

Claims 1, 4, 10, 12, 14, and 18-20 stand rejected under 35 USC §112, first paragraph. Applicants respectfully assert that the pending claims meet the requirements of 35 USC §112, first paragraph. However, to expedite prosecution Applicants have amended the claims 1, 18, and 20 as the Examiner recommends.

The Examiner rejected claims 1, 4, 10, 12, 14, and 18-19 under 35 USC §112, first paragraph for lack of teaching in the specification of a chelerythrine solvate or polymorph. Applicants have amended independent claims 1 and 18 to delete "solvate or polymorph."

The Examiner rejected claim 20 under 35 USC §112, first paragraph stating "the specification… does not reasonably provide enablement for preventing a subject from developing a CNS disorder by

administering chelerythrine." The Examiner considers the specification enabling for the treatment of mania by administration of chelerythrine. (Office Action dated May 14, 2008, page 2).

Applicants wish to point out that Claim 20, does not pertain to method of preventing a subject from developing a CNS disorder generally or even to a method of preventing bipolar disorder. Claim 20 pertains to a "method for preventing manic episodes in a bipolar patient." (emphasis added) Manic episodes are a well-known symptom of bipolar disorder. While there are no known compounds for preventing bipolar disorder in patients, drugs approved by the FDA for treating bipolar episodes prevent manic episodes. See Geddes et al. *Am. J. Psychiatry*, 161: 217-222 (2004), included in an IDS submitted with this response, which discusses the efficacy of Lithium in preventing manic episodes in bipolar patients.

Applicants respectfully request the Examiner to reconsider and withdraw the rejections under 35 USC §112, first paragraph in view of the foregoing amendments.

Claim Rejections Under 35 USC §102

Claims 1, 4, 10, and 18 –20 stand rejected under 35 USC 102(b) for anticipation by Birnbaum et al. (Society for Neuroscience Abstract, 2000). Birnbaum pertains only to local infusion of chelerythrine; it does not teach or suggest oral or systemic administration of chelerythrine. The pending claims pertain to oral or systemic administration of chelerythrine. Birnbaum does not anticipate the pending claims. Applicants respectfully request the Examiner to reconsider and withdraw the rejection under 35 USC §102(b).

Claim Rejections Under 35 USC §103

Claims 12 and 14 stand rejected under 35 USC 102(a) as unpatentable over Birnbaum in view of He (US Pat. No. 6,815,450), hereinafter "the '450 patent." Applicants agree that the '450 patent teaches chelerythrine as a PKC inhibitor and teaches in situ applications. Applicants disagree that given the teachings of the '450 patent a worker of ordinary skill would be motivated to modify the teachings of Birnbaum to include other modes of administration, including oral administration, to administer chelerythrine to a patient in need treatment for a working memory deficit or bipolar disorder.

The '450 patent provides methods for promoting regeneration of adult mammalian CNS axons. (Col. 2, lines 60-62.) The '450 inventors particularly contemplated regeneration of a spinal neuron axon that had been damaged by spinal injury. (Col. 3, lines 10-12.) Applicants wish to point out that spinal injury disrupts the blood brain barrier. Thus as a whole, the '450 patent is directed to methods in which the blood brain barrier is already open. In spite of this, the '450 patent discusses only in situ administration of PKC inhibitors in any detail and provides only examples of in situ administration of PKC inhibitors. The '450 patent discusses in the difficulty of transferring PKC inhibitors across the blood brain barrier and repeatedly discusses the desirability of in situ administration. When viewed as a whole the single mention of

pills and capsules at Col. 5, lines 10-11, which reads "Dosage units may be included in a variety of containers including capsules, pill, etc." cannot be seen as suggesting that PKC inhibitors would be expected to be effective when given orally or systemically for axon regeneration in the CNS. The '450 patent, when viewed as a whole, cannot be seen as suggesting PKC inhibitors administered orally or systemically would be effective for treating chronic CNS disorders in which the blood brain barrier is intact.

The section of the '450 patent cited by the Examiner (Col. 4, lines 3-6) teaches away from oral or systemic administration of PKC inhibitors. This section of the '450 patent is specifically directed to in situ applications. At column 4, lines 6-12 the '450 patent discusses particular techniques needed to transfer PKC inhibitors administered in situ (locally) across the blood brain barrier. These techniques include "disruption by surgery or injection, drugs which transiently open adhesion contact between CNS vaculature endothelial cells, and compounds which facilitate translocation through such cells." Thus the '450 patent acknowledges the difficulty of transferring PKC inhibitors across the blood brain barrier even when the inhibitors are administered in situ. One of ordinary skill reading this section of the '450 patent would appreciate the difficulty of transferring a PKC inhibitor across the blood brain barrier even when the inhibitor is administered in situ and be dissuaded from administering the PKC inhibitor orally or systemically for indications requiring penetration of the blood-brain barrier.

The '450 patent repeatedly discusses the desirability of local or in situ administration of a PKC inhibitor for axon regeneration. For example local administration is discussed in the "Summary of Invention Section" at Col. 2, lines 43-48 and in the "Description of Particular Embodiments of the Invention" at Col. 3, lines 10-15 and at Col. 4, lines 16-18. Direct injection into rat spinal cord is discussed in the Examples section at Col. 7, line 63 to Col. 8, line 12. Intrathecal injection into rat spinal subarachnoid space in discussed at Col. 9, line 55 to Col. 10, line 55.

The Examiner points to a section of the '450 patent that discusses forming pharmaceutically acceptable compositions of the inhibitors. These compositions in dosage units or bulk may be "included in a variety of containers including capsules, pill, etc." (Col. 5, lines 10-11). It is not possible to determine that the '450 patent inventor contemplates oral administration of PKC inhibitors for indications requiring transfer of the inhibitor across the blood brain barrier from this vague statement. Given the '450 inventors' repeated statements elsewhere in the patent that axon regeneration in the CNS is accomplished by local or in situ administration of a PKC inhibitor one of ordinary skill would not understand this the mention of pills and capsules in the '450 patent to be relevant to CNS administration. Rather one of ordinary skill would understand that the '450 patent inventor contemplates the use of pills or capsules for axon regeneration outside the CNS and not for indications that require transfer of PKC inhibitors across the blood brain barrier.

Additionally the mention of pills and capsules in the '450 patent cannot form the basis for an obviousness rejection for a method of treatment in which chelerythrine must cross the blood brain barrier because a worker of ordinary skill, reading the '450 patent would not have known how to transfer chelerythrine across the blood brain barrier. According to PTO guidelines " .. the focus when making a determination of obviousness should be on what a person of ordinary skill in the pertinent art would have known at the time of the invention, and on what such a person would have reasonably expected to have been able to do in view of that knowledge." Examination Guidelines for Determining Obviousness Under 35 USC in View of the Supreme Court Decision in *KSR International Co. v. Teleflex Inc.*, Federal Register Vol. 72, No. 195, p. 57526. The statements at Col. 4, lines 3-6 clearly demonstrate that the '450 patent inventors understood PKC inhibitors would not penetrate the blood brain barrier even for in situ applications. The non-invasive techniques recommended in the '450 patent, "drugs which transiently open adhesion contact between CNS vasculature endothelial cells, and compounds which facilitate translocation through such cells," do not exist for the treatment of chronic conditions, such as those claimed. Use of blood brain barrier disruption for the treatment of chronic conditions is unworkable because keeping the blood brain barrier open more than transiently is toxic to the brain and would result in brain damage to the patient.

Thus a person of skill in the art, reading Birnbaum et al. 2000, would not have found it obvious in view of the '450 patent to administer any PKC inhibitor, much less chelerythrine, orally or non-systemically for indications requiring PKC inhibition in the brain. Birnbaum pertains only to local infusion of chelerythrine directly into the brain; it does not teach or suggest oral or systemic administration of chelerythrine. Indeed, Birnbaum, Arnsten and colleagues infused chelerythirne directly into the brain because the field at this time indicated that direct infusion would be necessary for brain activity. The '450 reference, when viewed as a whole, does not suggest oral or systemic administration of PKC inhibitors. Birnbaum and the '450 patent do not separately or in combination teach or suggest the oral or systemic administration of PKC inhibitors for treatment of conditions requiring the inhibitor to cross the blood brain barrier. Applicant's discovery that chelerythrine could be given orally or systemically to treat bipolar disorder and working memory deficits was completely unexpected.

Applicants respectfully request the Examiner to reconsider and withdraw the rejections under 35 USC §103.

If there are any charges with respect to this amendment, or otherwise, please charge them to Deposit Account No. 06-1130 maintained by applicant's attorneys.

Respectfully submitted,
CANTOR COLBURN LLP
Applicant's Attorneys

Date: November 14, 2008
Address: CANTOR COLBURN, LLP

55 Griffin Road South
Bloomfield, CT 06002
Telephone: (860) 286-2929
PTO Customer No.: 23413

By: /Leslie-Anne Maxwell/
Leslie-Anne Maxwell, Ph.D.
Registration No. 44,778